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Clinical characteristics of patients with anti-EJ antisynthetase syndrome associated interstitial lung disease and literature review

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ABSTRACT

Aim: Interstitial lung disease (ILD) is an extra-muscular manifestation of antisynthetase syndrome (ASS). The aim of this study is to analyze the clinical characteristics of anti-EJ associated ILD in a large cohort of patients.
Methods: Retrospective cohort study of patients with anti-EJ associated ILD. All available data of clinical and laboratory characteristics, pulmonary function tests, laboratory parameters, high resolution computed tomography (HRCT) and treatment were collected and analyzed from medical records.
Results: We identified 51 subjects. Average age at diagnosis was 55.6 years. Thirty-two of 51 patients were female. Concurrent autoantibodies against Ro52 were seen in 92.2% patients studied. HRCT patterns were mainly non-specific interstitial pneumonia (NSIP). The predominant myositis subset was amyopathic dermatomyositis (ADM) (41.2%) followed by dermatomyositis and polymyositis. Thirty-four patients improved on corticosteroids alone or in combination with immunosuppressive drugs as treatment and ten patients were stabilized. However, eleven patients (21.6%) initially improved during 12.0 ± 4.4 months, then progressively recurred despite steroid treatment (mean prednisone dose 11.6 ± 3.5 mg). The recurrence group included a significantly higher proportion of patients with NSIP pattern ($p < 0.05$). In the literature review the most common manifestations of anti-EJ ASS were ILD (89.3%) and myositis (58.9%).
Conclusion: ILD are common features of the anti-EJ ASS. Patients with anti-EJ ILD often had an onset of ILD with lower lung-predominant opacities and NSIP. Although the disease responded well to the initial combination therapy of corticosteroid and immunosuppressant, recurrence was frequent. NSIP pattern was significantly more frequent in the recurrence group.

1. Introduction

Antisynthetase syndrome (ASS) is defined by the occurrence of anti-aminoacyl tRNA-synthetase (anti-ARS) antibodies and associated types of autoimmune manifestations, mainly myositis [1]. The autoimmunity accounts for important clinical manifestations, such as interstitial lung disease (ILD), fever, arthritis, Raynaud's phenomenon (RP) and mechanic's hand [2]. At present, ten anti-ARS antibodies have been identified: anti-Jo-1 (histidyl), anti-PL7 (threonyl), anti-PL12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginyl), anti-ZO (phenylalanyl), anti-YRS/HA (tyrosyl), anti-SC (lysyl) and anti-JS (glutaminyl) [3,4]. The most commonly encountered antibody is anti-Jo-1 that accounts for up to 60–80% [5]. Although, anti-EJ antibody, which is generally less common than anti-Jo-1 antibody, it may have a higher prevalence in some case series of patients with ILD positive of anti-ARS antibodies [6,7].

ILD is a major contributor to morbidity and mortality, and recent data suggest that different ASS phenotypes could be related to incidence and severity of ILD [7]. The pulmonary damage may be irreversible, which is consistent with early scarring of the interstitium. However, there are only a few reports describing the detailed clinical features of patients with ILD with positive-anti EJ antibody [6–8]. The aim of this

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retrospective study was to define the clinical, radiological, treatment and follow-up features of patients with anti-EJ associated ILD.

2. Methods

2.1. Study subjects and diagnostic criteria

Our study included 51 consecutive patients diagnosed with anti-EJ associated ILD between February 1, 2017 and April 30, 2019 at the Department of respiratory and critical care medicine, Nanjing Drum Tower Hospital, China. The study protocol was approved by the Institutional Review Board of Nanjing Drum Tower Hospital (2016-138-01). Written informed consent was waived because of the retrospective chart review design of this study. All available data regarding clinical characteristics, pulmonary function tests (PFT), laboratory parameters, high resolution computed tomography (HRCT), treatment and disease course were collected from the patient files.

The diagnosis of anti-EJ ASS was made by the presence of anti-EJ on serology accompanied by key clinical features, including ILD and/or polymyositis (PM)/dermatomyositis (DM) and evaluated by an expert panel of rheumatologist, respiratory physicians and radiologist. RP, arthritis, fever and mechanic's hands supported the diagnosis, but their presence was not mandatory [9]. The patients with PM/DM fulfilled the criteria defined by Bohan and Peter [10,11], and clinically amyopathic DM (ADM) fulfilled the Sontheimer's criteria [12]. The diagnosis of ILD was defined as the presence of radiographic abnormalities on HRCT scans of the lungs with respiratory symptoms [13]. The presence of ILD was evaluated at a multidisciplinary team discussion with the presence of an expert ILD radiologist and expert ILD respiratory physicians. To compare the characteristics between ASS-ILD patients with anti-EJ antibody and those with anti-Jo-1 antibody. We collected the medical records of anti-Jo-1 associated ILD exactly during the same period of time between February 1, 2017 and April 30, 2019.

2.2. Detection of serum autoantibodies

Myositis-specific and myositis-associated autoantibody (anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-SRP, anti-Jo-1, antiPL-7, anti-PL-12, anti-EJ, and anti-OJ) were identified by line immunoassay (Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany) according to the manufacturer's protocol. The positive control was provided by the test kit and the sample buffer was provided as a negative control. To exclude false-positive cases, we included only patients who repeatedly tested positive for anti-EJ. This commercial line blot assay for myositis diagnosis was assessed on its diagnostic accuracy against RNA immunoprecipitation in a multicenter cohort of patients with idiopathic inflammatory myopathies (IIM) [14]. The overall specificity of the line blot is 92% compared to the 95% specificity of RNA immunoprecipitation. Sensitivity of the line blot is 38% compared to 43% of RNA immunoprecipitation. Concordance rate between the line blot and RNA immunoprecipitation is 91% [14]. Antinuclear antibodies (ANA) and extractable nuclear antigens (ENA) were assessed by ELISA.

2.3. Clinical data

Demographic, therapeutic, clinical and laboratory data were obtained following a systematic review of patient charts. The following parameters were analyzed as clinical manifestations: constitutional symptoms; skin changes (heliotrope rash, Gottron's sign, RP, mechanic's hands); joint involvement (arthralgia and/or arthritis); muscular involvement (myalgia, muscle weakness); the presence of cough and dyspnea. ILD was diagnosed based on chest HRCT. Laboratory data consisted of creatine kinase (CK), lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

2.4. Radiological analysis

Baseline HRCT images were obtained from all the 51 patients. All images were reviewed independently by two experienced radiologists without any prior knowledge of the clinical and pathological information. The following HRCT findings were coded as present or absent in each zone: reticulation, ground-glass opacity (GGO), consolidation, bronchovascular thickening, traction bronchiectasis, and honeycombing. The upper lung zone was located at and above the level of the aortic arch. The middle zone was located between the aortic arch and the inferior pulmonary veins. The lower lung zone was located at and below the inferior pulmonary veins [15]. Radiological assessment was based on the 2013 American Thoracic Society classification of idiopathic interstitial pneumonia [16], the interstitial pneumonia with autoimmune features (IPAF) criteria [17] and the recommendations of the Fleischner Society [18]. Based on the proposed criteria of the guidelines, nonspecific interstitial pneumonia (NSIP) pattern was defined as irregular reticular opacities with traction bronchiectasis and bronchiolectasis, peri-bronchovascular extension, frequently associated with bilateral ground-glass attenuation; organizing pneumonia (OP) pattern was defined as patchy and often migratory consolidation in a subpleural, peribronchial, or bandlike pattern, commonly associated with GGO; NSIP with OP overlapping was defined as basal predominant consolidation, often peri-diaphragmatic, associated with traction bronchiectasis, reticular abnormality or lower lobe volume loss. Usual interstitial pneumonia (UIP) pattern was characterized by features of honeycombing, reticular pattern with peripheral traction bronchiectasis or bronchiolectasis, subpleural and basal predominance, and absence of features to suggest an alternative diagnosis. A CT pattern comprising of the aforementioned criteria for UIP pattern except honeycombing change was defined as probable UIP pattern [19]. Both UIP and probable UIP were grouped together for the purposes of this analysis. Disagreements between the two radiologists were resolved by consensus.

2.5. Outcome of ILD

Patients underwent clinical evaluation every 3–6 months. The duration of follow-up was noted. The last HRCT which was available in our system was considered as the end point of follow-up in patients with multiple examinations. Follow-up CT findings were compared with the initial findings for the extent of the abnormalities. Two radiologists evaluated the chest HRCT. ILD course assessed by HRCT was categorized as improved, stability, or deterioration by serial HRCT assessment according to the study radiologists' interpretation, using the method by Akira et al. [20]. Deterioration and improved of the overall disease extent were respectively defined by an increase or decrease of at least 10% of the overall disease extent, whereas stability was defined by changes of less than 10% [20,21]. The recurrence of ILD was defined by 2 or more of the following: (1) deterioration in dyspnea or PM/DM-related extrapulmonary symptoms; (2) increase in ILD-related parenchymal abnormality on chest HRCT or radiograph; and/or (3)≥ 10% decrease in percent predicted forced vital capacity (%FVC), ≥15% decrease in percent predicted diffusing capacity of the lung for carbon monoxide (%DLCO), ≥10 mmHg decrease in arterial oxygen pressure (PaO2), or a ≥4% decrease in peripheral capillary oxygen saturation (SpO2); and/or (4) new development of PM/DM-related extrapulmonary manifestations [22].

2.6. Literature review

We searched the English language literature in the PubMed database (National Library of Medicine, Bethesda, MD) for related articles published up to April 2019, using the following key words: "EJ antibody," "anti-EJ," "anti-glycyl-tRNA synthetase," and "antisynthetase syndrome" [6–8,23–30]. Studies were excluded if they included only one anti-EJ case or lacked clinical features.

2.7. Statistical analysis

Qualitative data are presented as numbers and percentage, and quantitative data as mean and standard deviation (SD) or median and interquartile range (IQR) depending on skewness of the data. Association between the presence of anti-EJ antibodies and qualitative variables was assessed using the chi-squared and Fisher exact tests, depending on the expected cell count (more or less than 5, respectively). All statistical analyses were performed with SPSS 13.0 software (SPSS, Chicago, IL). Significance was set at a p value of less than 0.05.

3. Results

3.1. Demographic, clinical, and laboratory features

Fifty-one patients with anti-EJ associated ILD were identified between 2017 and 2019. Clinical features of the 51 patients are summarized in Table 1. Median age at the time of diagnosis was 55.6 years (range 31–83 years). Nine (17.6%) patients were current or former smokers. Median duration of symptoms before diagnosis was 12.1 months (range 0.5–120 months) from the first visit at the rheumatology or respiratory outpatient clinic. Thirty-two patients (62.7%) were female. All were Chinese. PM was diagnosed in 10 (19.6%) patients, DM in 11 (21.6%), and ADM in 21 (41.2%) patients.

Cough and dyspnea were the initial symptom, and ILD was the presenting manifestation, in all 51 subjects. The most common extrapulmonary symptoms were mechanic's hands (22/51, 43.1%), muscle weakness (21/51, 41.2%), fever (20/51, 38.5%), Gottron's sign (13/51, 25.5%), myalgia (10/51, 19.6%), joint involvement (8/51, 15.7%), heliotrope symptoms (7/51, 13.7%), and RP (2/51, 3.9%).

Serum creatine kinase >3000 U/L was not found in all anti-EJ positive patients. Thirty-nine subjects (76.5%) had available baseline PFT. The majority showed restriction (97.4%) with mean FVC at 59.2% and mean DLCO at 50.1% of predicted (Table 1).

ANA were positive (title≥1:80 dilution) in 43/51 patients (84.3%). ENA were positive in 47/51 patients (92.2%). Anti-Ro52 antibody was detected in 47 patients possessing anti-EJ (92.2%). Six of 51 anti-EJ associated ILD also resulted positive for anti-Ro/SSA antibodies (three of them in addition positive for anti-La/SSB) and fulfilled the criteria for an associated Sjögren's syndrome [31]. Anti-AMA-M2 and Anti-nRNP/Sm antibody were present in one patient (2.0%), respectively.

3.2. Radiological findings

All subjects had available baseline HRCT images that were reviewed by two independent radiologists. In all 51 patients with ILD, pulmonary involvement was confirmed by HRCT, which showed various radiologic patterns. The HRCT findings are described in Table 2. All findings were observed in both lungs. The most common pattern was NSIP (n = 27, 52.9%), followed by NSIP/OP (n = 12, 23.5%), OP (n = 11, 21.6%). UIP pattern was observed in 1 (2.0%) subject. Signs of GGO were documented in 47 of the 51 patients (92.2%), traction bronchiectasis in 43 (84.3%), reticulation in 37 (72.5%), consolidation in 35 (68.6%), bronchovascular thickening in 35 (68.6%), and honeycombing in 2 (3.9%). Forty-four subjects had available follow-up HRCT chest images for review.

3.3. Clinical course and treatment response

Details on the clinical courses and therapy of the 51 patients are shown in Table 3. All but 1 received corticosteroid therapy. Forty-three patients (84.3%) were treated with combination therapy of corticosteroid and immunosuppressant as the initial treatment while six were given corticosteroid monotherapy due to combined inflammation. The following treatment options were used either alone or in combination: glucocorticoids (98.0%), cyclophosphamide (39.2%), cyclosporine (21.6%), tacrolimus (17.3%), methotrexate (1.9%), mycophenolate mofetil (1.9%) and azathioprine (1.9%).

The mean duration of follow-up was 11.3 months (range, 1–29 months). The treatment response was evaluated in 44 of 51 patients. ILD improved in 34 patients and stabilized in 10; however, in 11 patients, it initially improved during mean 12.0 months (range, 6–18 months), then progressively recurred despite treatment. No patient died during the follow-up.

Age, gender, smoking history, laboratory findings and treatments were not significantly different in the recurrence and non-recurrence groups (Table 4). The proportion of patients with NSIP pattern was significantly higher in the recurrence group (81.8% vs. only 45.5% in the non-recurrence group, $p = 0.044$). All the eleven patients were still on steroid treatment (mean prednisone dose 11.6 ± 3.5 mg; range 5–15 mg/day) when the recurrence occurred. The mean time to relapse was

Table 1
Patient baseline demographics and disease characteristics.

Characteristics	Results
Total subjects	51
Female	32 (62.7)
Age at diagnosis, yrs, mean (SD)	55.6 (10.9)
Smoking status (current or former/never smoker)	9/42
Median duration of symptoms before diagnosis, months, median (IQR)	12.1 (0.5–120)
Idiopathic inflammatory myopathy	42 (82.4)
DM subset	11 (21.6)
PM subset	10 (19.6)
ADM subset	21 (41.2)
Overlap with other CTD	6 (11.8)
Sjögren's syndrome	6 (11.8)
Clinical manifestations	
Fever	20 (38.5)
Cough	52 (100)
Dyspnea on exertion	52 (100)
Skin involvement	
Heliotrope	7 (13.7)
Gottron's sign	13 (25.5)
Raynaud's phenomenon	2 (3.9)
Mechanics hands	22 (43.1)
Joint involvement	
arthralgia and/or arthritis	8 (15.7)
Muscular involvement	
Myalgia	10 (19.6)
Muscle weakness	21 (41.2)
Laboratory findings	
Level of Maximum CK, U/L, mean (IQR)	383.4 (16–2052)
Level of LDH, U/L, mean (IQR)	310.8 (166–839)
Level of ESR, mm/h, mean (IQR)	35.1 (4–86)
Level of CRP, mg/L, mean (IQR)	17.2 (1.2–117)
Positive ANA (title≥1:80 dilution)	43 (84.3)
Positive ENA	47 (92.2)
Ro-52	47 (92.2)
Pulmonary function test	
FEV1, % predicted, mean (IQR)	62.9 (33.8–97.6)
FVC, % predicted, mean (IQR)	59.2 (36.6–97.9)
DLCO, % predicted, mean (IQR)	50.1 (19.7–95.2)

Values are n (%) unless otherwise specified.
[a]ADM vs DM and PM, $p < 0.05$. [b]PM vs ADM and DM, $p < 0.05$. [c]ADM vs DM, $p = 0.033$. [d]ADM vs PM, $p = 0.027$. [e]ADM vs DM and PM, $p < 0.001$. [f]ADM vs DM, $p = 0.003$. [g]PM vs ADM and DM, $p < 0.05$. SD: standard deviation; IQR: interquartile range; CTD: connective tissue disease; DM: Dermatomyositis; PM: Polymyositis; ADM: Amyopathic dermatomyositis; CK: creatine kinase; LDH: actatedehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: anti-nuclear antibody; ENA: extractable nuclear antigen; FEV1: forced expiratory volume in the first second; FVC: forced expiratory volume; DLCO: diffusing capacity of the lung for carbon monoxide.

Table 2
Features on radiological imaging.

	EJ, n = 51	Jo-1, n = 84	*p*
HRCT pattern at presentation			
NSIP	27 (52.9)	54 (64.3)	0.192
OP	11 (21.6)	18 (21.4)	0.985
NSIP-OP	12 (23.5)	12 (14.3)	0.173
UIP	1 (2.0)	0	0.378
HRCT predominance of findings			
Upper lobes	0	0	
Lower lobes	25 (49.0)	29 (34.5)	0.096
Diffuse	26 (51.0)	55 (65.5)	0.096
HRCT findings			
Traction bronchiectasis	43 (84.3)	60 (71.4)	0.088
Ground glass opacities	47 (92.2)	82 (97.6)	0.199
Consolidation	35 (68.6)	68 (81.0)	0.103
Reticulation	37 (72.5)	78 (92.9)	0.001
Bronchovascular thickening	35 (68.6)	22 (26.2)	<0.001
Honeycombing	2 (3.9)	3 (3.6)	>0.999

Values are n (%) unless otherwise specified.
DM: Dermatomyositis; PM: Polymyositis; ADM: Amyopathic dermatomyositis; HRCT: high resolution computed tomography; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; UIP: usual interstitial pneumonia.

Table 3
Treatment and clinical course of the entire cohort.

Characteristic	EJ, n = 51	Jo-1, n = 84	*p*
No immunosuppressive therapy	1 (1.9)	6 (7.1)	0.188
Initial treatment			
CS oral only	2 (3.9)	4 (4.8)	>0.999
CS pulse + oral	4 (7.8)	7 (8.3)	0.920
CS (pulse and/or oral)+CsA	11 (21.6)	28 (33.3)	0.144
CS (pulse and/or oral)+Tac	9 (17.3)	13 (15.5)	0.741
CS (pulse and/or oral)+CY (oral and/or iv)	20 (39.2)	18 (21.4)	0.026
CS (pulse and/or oral)+AZA	1 (1.9)	1 (1.2)	>0.999
CS (pulse and/or oral)+MTX	1 (1.9)	0	0.378
CS (pulse and/or oral)+MMF	1 (1.9)	2 (2.4)	>0.999
CS (pulse and/or oral)+CsA or Tac + CY (oral and/or iv)	1 (1.9)	5 (6.0)	0.408
Duration of Treatment in months, median (IQR)	11.3 (1-29)	14.3 (1-32)	0.064
Response of ILD to Treatment			
Unknown	7 (13.7)	30 (38.1)	
Worsening	0	1 (1.2)	>0.999
Improved	34 (66.7)	41 (48.8)	0.043
Stability	10 (19.6)	12 (14.3)	0.417
Recurrence	11 (21.6)	20 (23.8)	0.764
Recurrence time, median (IQR)	12.0 (6-18)	10.7 (2-20)	0.609
PSL dose at the recurrence (mg/day)	11.6 ± 3.5	14.4 ± 9.8	0.078

Values are n (%) unless otherwise specified.
Abbreviation: CS: corticosteroid; CsA: cyclosporine A; Tac: tacrolimus; CY: cyclophosphamide; iv: intravenous administration; AZA: azathioprine; MTX: methotrexate; MMF:mycophenolate mofetil; IQR: interquartile range; ILD: interstitial lung disease; PSL:prednisolone.

12.0 ± 4.4months (range, 6–18months). All patients were treated with increased steroid dose when relapse occurred, and the mean prednisone equivalent dose at that time was 28.3 ± 4.1 mg/day.

3.4. Comparison with clinical findings of anti-Jo-1 patients

Anti-Ro52 antibody was detected in 74 patients possessing anti-Jo-1 (74/84, 88.1%). The prevalence of anti-Ro52 antibody was not significantly different in anti-EJ and anti-Jo-1 groups. NSIP was also the most common HRCT pattern in anti-Jo-1 ILD. The prevalence of reticulation was higher in anti-Jo-1 associated ILD patients ($p = 0.001$). While bronchovascular thickening occurred more frequently in anti-EJ ILD ($p < 0.001$). Compared to anti-Jo-1 ILD, we have mainly used cyclophosphamide as the first-line therapy for anti-EJ ILD over the study period ($p = 0.026$). Improvement was more frequent in the group of anti-EJ at initial treatment of ILD ($p = 0.043$).

Table 4
Comparison of clinical characteristics between non-recurrence and recurrence group in anti-EJ associated ILD.

Characteristic	Non-recurrence group, n = 33	Recurrence group, n = 11	*p*
Female	20 (60.6)	9 (81.8)	0.282
Age at diagnosis, yrs, mean (SD)	57.1 (12.2)	54.1 (8.0)	0.447
Smoking status (current or former/never smoker)	6/27	1/10	0.475
Disease duration, months, median (IQR)	14.0 (0.5–120)	7.3 (0.7–24)	0.524
ADM	12 (36.4)	5 (45.5)	0.592
DM	7 (21.2)	3 (27.3)	0.678
PM	7 (21.2)	1 (8.3)	0.367
Clinical manifestations			
Fever	15 (45.5)	5 (45.5)	0.867
Heliotrope	3 (9.1)	3 (27.3)	0.154
Gottron's sign	8 (24.2)	7 (63.6)	0.028
Raynaud's phenomenon	1 (3.0)	0	0.559
Mechanics hands	14 (42.4)	5 (45.5)	0.861
Arthralgia and/or arthritis	4 (12.1)	3 (27.3)	0.234
Myalgia	5 (15.2)	2 (16.7)	0.812
Muscle weakness	8 (24.2)	1 (8.3)	0.411
Laboratory findings			
Level of Maximum CK, U/L, mean (IQR)	459.8 (20–2046)	341.1 (16–1171)	0.439
Level of LDH, U/L, mean (IQR)	330.1 (166–839)	286 (190–419)	0.111
Level of ESR, mm/h, mean (IQR)	40.2 (4–83)	28.6 (6–86)	0.187
Level of CRP, mg/L, mean (IQR)	20.2 (1.8–117)	6.6 (1.2–21.8)	0.131
Ro-52, n (%)	30 (90.9)	10 (90.9)	>0.999
Pulmonary function test			
FEV1, % predicted, mean (IQR)	63.3 (33.8–97.6)	62.5 (38.2–77.7)	0.972
FVC, % predicted, mean (IQR)	58.7 (36.7–97.9)	60.4 (42.4–79.9)	0.723
DLCO, % predicted, mean (IQR)	50.2 (38.2–95.2)	52.7 (31.7–67.3)	0.672
No immunosuppressive therapy	1 (3.0)	0	>0.999
Initial treatment			
CS oral only	1 (3.0)	0	>0.999
CS pulse + oral	4 (12.1)	1 (8.3)	>0.999
CS (pulse and/or oral)+CsA	7 (21.2)	3 (25.0)	0.692
CS (pulse and/or oral)+Tac	5 (15.2)	3 (25.0)	0.391
CS (pulse and/or oral)+CY (oral and/or iv)	13 (39.4)	3 (25.0)	0.719
CS (pulse and/or oral)+AZA	0	1 (8.3)	0.250
CS (pulse and/or oral)+MMF	1 (3.0)	0	>0.999
CS (pulse and/or oral)+CsA or Tac + CY (oral and/or iv)	1 (3.0)	1 (8.3)	0.442
HRCT pattern			
NSIP	15 (45.5)	9 (81.8)	0.044
OP	8 (24.2)	2 (18.2)	>0.999
NSIP-OP	9 (27.3)	0	0.085
UIP	1 (3.0)	0	>0.999

Values are n (%) unless otherwise specified.
ILD: interstitial lung disease; IQR: interquartile range; ADM: amyopathic dermatomyositis; DM: dermatomyositis; PM: polymyositis; CK: creatine kinase; IQR: interquartile range; LDH: actatedehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; FEV1: forced expiratory volume in the first second; FVC: forced expiratory volume; DLCO: diffusing capacity of the lung for carbon monoxide. CS: corticosteroid; CsA: cyclosporine A; Tac: tacrolimus; CY: cyclophosphamide; iv: intravenous administration; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil; HRCT: high resolution computed tomography; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; UIP: usual interstitial pneumonia.

3.5. Literature review

We identified 112 additional cases of anti-EJ ASS in the literature. The main clinical manifestations were ILD in 100 (89.3%) patients and myositis in 66 (58.9%). The prevalence of other signs and symptoms of anti-EJ ASS is summarized in Table 5.

4. Discussion

Positive test results for anti-EJ antibodies are particularly rare in patients with ILD [7]. Compared to the analysis on clinical characteristics associated with anti-Jo-1, which is the most prevalent myositis-specific autoantibody (MSA), much less information is available on those associated with anti-EJ antibodies other than anti-Jo-1 because of their low prevalence [5,6]. Therefore, the specific characteristics of anti-EJ associated ILD as opposed to the more common anti-Jo-1 ASS characteristics are not well described. We retrospectively evaluated the clinical, radiological, pathological features and clinical courses of 51 patients with ILD in anti-EJ antibodies positive.

Although patients with antisynthetase antibodies share many common clinical features, several investigators have reported on the heterogeneity of ASS. Anti-Jo-1, anti-EJ, and anti-PL-7 belong to the myositis-related subgroup, since myositis was found in at least half of the patients with these anti-ARS antibodies [24,32]. Our series agreed with previous reports describing a relationship of myositis with anti-EJ. Additionally, more than one-third of patients with anti-EJ associated ILD were diagnosed with ADM. ADM is recognized as a distinct subgroup of DM with the typical skin rash of classic DM, but without muscle involvement [7]. In our study, prevalence of ADM was found 41.2% (21/51) in anti-EJ associated ILD patients. However, the ratio of PM and DM was much lower to 21.6% and 19.6%, respectively. Similar to the series reported in Hamaguchi Y et al. [24], our series also clearly showed a low prevalence of arthritis symptoms; other skin manifestations, including RP and typical heliotrope rash, are also not common. Mechanic's hands and Gottron's sign may be observed more common in anti-EJ ILD patients.

Anti-Ro52 is now recognized as one of the myositis-associated autoantibodies. This specificity has been described as a serological marker for Sjögren syndrome, but patients with different anti-ARS in combination with anti-Ro52 appear to be associated with distinctive clinical subsets. Frequency of anti-Ro52 antibodies was significantly higher in the anti-ARS-positive group (59%) than in the anti-ARS negative group [33]. Previous studies found anti-Ro52 reactivity in 52.6–65% of anti-Jo1-positive sera [25,34,35]. In our study, the frequency of anti-Ro52 antibody in anti-EJ and anti-Jo-1 ILD is respectively 92.2% and 88.1%. No significant difference was found. Moreover, anti-Ro52 has been shown to be associated closely with pulmonary manifestations. Other authors have found that the presence of anti-Ro52 causes more severe ILD in ASS [36,37]. One previous study suggested that ASS patients who manifested coexistence with anti-Ro52 antibody experienced higher frequency of rapidly progressive ILD and mortality than those without anti-Ro52 antibody. But there was no positive anti-Ro52 antibody significant difference in our recurrence and no-recurrence groups.

In the previous studies, near 90% of patients with positive-anti-EJ antibodies show ILD complications [5–7,18–25]. The most common radiologic pattern found in our cohort was NSIP, a finding similarly described in the literature in association with other ASS-ILD. UIP CT pattern was very rare in anti-EJ ILD. Chest CT revealed GGO, consolidation, traction bronchiectasis, reticulation and bronchovascular thickening distributed in lower lung fields and lack of honeycombing. In ILD patients with anti-Jo-1, the predominantly inferior location was frequent, whereas honeycombing was also rare. There was no significant difference in the prevalence of honeycombing, traction bronchiectasis, GGO and consolidation between anti-EJ and anti-Jo-1 subjects. While the prevalence of bronchovascular thickening occurred more frequently

Table 5
Summary of the studies of anti-EJ ASS.

First Author, Ref.	n	F/M	Myositis	ADM	DM	PM	overlap	ILD	High CK	Coexistence of Ro52	Fever	Cough	Dyspnoea	Heliotrop	Gottron's sign	RP	MH	Arthritis	Myalgia	Muscle weakness
Yang [7]	4	2/2	4	0	1	3	0	4	4	4	2	ND	ND	0	1	1	1	3	ND	4
Li [19]	13	ND	13	0	12	1	ND	12	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Shi [18]	19	16/3	10	ND	ND	ND	4	19	ND	10	ND	ND	ND	3	6	1	9	5	10	8
Sasano [6]	12	7/5	6	0	2	4	0	12	3	ND	5	11	7	0	ND	3	3	5	7	ND
Giannini [20]	3	3/0	2	0	0	2	0	3	2	ND	1	1	2	0	0	1	0	2	0	2
Johnson [21]	2	1/1	2	0	0	2	0	0	ND	ND	ND	ND	1	0	0	0	0	ND	1	0
Schneider [22]	4	3/1	0	ND	ND	ND	1	4	0	0	0	ND	2	0	0	3	3	1	0	0
Hane [23]	5	4/1	3	0	2	1	0	2	ND	2	ND	ND	ND	1	2	ND	ND	ND	ND	3
Hamaguchi [17]	38	32/6	21	7	14	5	6	35	ND	9	15	ND	ND	8	12	5	11	9	ND	15
Watanabe [5]	6	2/4	ND	ND	ND	ND	3	4	ND	1	0	ND	ND	0	0	0	1	2	ND	ND
Targoff [16]	6	3/2	5	0	5	0	1	5	2	ND	4	ND	3	1	2	4	2	5	3	3

*(Table 5 Breakdown): ASS: antisynthetase syndrome; ADM: Amyopathic dermatomyositis; DM: Dermatomyositis; PM: Polymyositis; ILD: interstitial lung disease; CK: creatine kinase; RP: Raynaud phenomenon; MH: mechanic's hands, ND: no data.

in anti-EJ ILD. We have shown that patients with anti-EJ ILD had an onset of ILD with lower-lung predominant opacities on HRCT, NSIP or OP, NSIP-OP patterns, and good response for initial steroid therapy, although relapses were frequent with corticosteroid combined with immunosuppressive drugs. We further found that a pattern of NSIP on HRCT scan was significantly more frequent in the recurrence group.

In our study, EJ-ILD was improved or stabilized in all, thus suggesting a good response to the initial treatment. The treatment response of anti-EJ ILD and the rate of recurrence were similar to those previously reported for ARS-ILD [5–7,18–25]. Improvement was observed more frequent in anti-EJ group in comparison to anti-Jo-1 at initial treatment of ILD. Although the initial treatment for anti-EJ ILD was effective for most of the patients, ILD relapsed in nearly one third of them during oral corticosteroid tapering. There was no significant difference in the recurrence rate between anti-EJ and anti-Jo-1 groups. Corticosteroid with/without immunosuppressants therapy is the first-line treatment for myositis as well as ASS-ILD. We have mainly used cyclophosphamide as the first-line therapy for EJ-ILD over the study period, while cyclosporine for Jo-1-ILD first-line therapy. The difference of more cyclophosphamide using in EJ-ILD rather than in Jo-1-ILD maybe due to some cases were not firstly diagnosed with EJ-ILD but Sjögren's syndrome, IPAF and RA respectively before the myositis autoantibody testing finished. No difference in EJ-ILD recurrence was noted among different immunosuppressants types. As the results shown in our study, the rate of recurrence was 21.6%, but all of the recurred patients showed improvement after re-treatment with steroids, and none of the patients in this subgroup died. In our study, the mean duration from the induction to the recurrence was 11.3 months. The median dose of PSL at anti-EJ ILD recurrence was 11.6 mg. The optimal dose and duration of glucocorticoid therapy is still unclear because most studies of patients with anti-EJ associated ILD used a variety of regimens in a small number of patients.

Our study has a few limitations. First, it was a retrospective study, and the sample size is relatively small. However, it seems to be the largest anti-EJ ILD cases at present. Second, since this study was performed in a specialized single-center for the respiratory diseases , there might be a selection bias for the diagnosis of PM/DM and ADM at the initial visit.

5. Conclusion

In conclusion, our findings suggested that anti-EJ ILD was prevalent in patients with IIM, especially in patients with ADM. Patients who presented with mechanics hands and Gottron's sign tended to have a higher frequency of anti-EJ associated ILD. Furthermore, anti Ro52 antibodies were frequently detected with anti-EJ associated ILD. The diseases recurred frequently within NSIP pattern. The increase of the dose of corticosteroid should be on the list of options to improve the recurrence of anti-EJ ILD. We need to conduct long term observation to assess clinical behavior and prevent complications of EJ-ILD.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yin Liu: Writing - original draft, Writing - review & editing. **Xiaoqing Liu:** Data curation. **Miaomiao Xie:** Data curation. **Zhiyong Chen:** Methodology, Resources. **Jian He:** Writing - original draft, Writing - review & editing. **Zhengge Wang:** Writing - original draft, Writing - review & editing. **Jinghong Dai:** Writing - original draft. **Hourong Cai:** Writing - original draft.

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References

[1] M. Mahler, F.W. Miller, M.J. Fritzler, Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensivereview, Autoimmun. Rev. 13 (2014) 367–371.
[2] R.W. Hallowell, S.K. Danoff, Interstitial lung disease associated with the idiopathic inflammatory myopathies and the antisynthetase syndrome: recent advances, Curr. Opin. Rheumatol. 26 (2014) 684–689.
[3] M. Hirakata, Autoantibodies to aminoacyl-tRNA synthetases, Intern. Med. 44 (2005) 527–528.
[4] L.J. Witt, J.J. Curran, M.E. Strek, The diagnosis and treatment of antisynthetase syndrome, Clin. Pulm. Med. 23 (2016) 218–226.
[5] R. Aggarwal, E. Cassidy, N. Fertig, D.C. Koontz, M. Lucas, D.P. Ascherman, et al., Patients with non-Jo-1 antitRNAsynthetase autoantibodies have worse survival than Jo-1 positive patients, Ann. Rheum. Dis. 73 (2014) 227–232.
[6] K. Watanabe, T. Handa, K. Tanizawa, Y. Hosono, Y. Taguchi, S. Noma, et al., Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias, Respir. Med. 105 (2011) 1238–1247.
[7] H. Sasano, E. Hagiwara, H. Kitamura, Y. Enomoto, N. Matsuo, T. Baba, et al., Long-term clinical course of anti-glycyl tRNA synthetase (anti-EJ) antibody-related interstitial lung disease pathologically proven by surgical lung biopsy, BMC Pulm. Med. 16 (2016) 168.
[8] Y. Yang, Y. Liu, L. Huang, L. Wang, K. Liu, M. Liu, et al., Clinical features and cytokine profile in myositis patients with anti-EJ autoantibodies detected by a novel immunoprecipitation assay, BioMed Res. Int. 2019 (2019), 1856180.
[9] G.R. Connors, L. Christopher-Stine, C.V. Oddis, S.K. Danoff, Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 138 (2010) 1464–1474.
[10] A. Bohan, J.B. Peter, Polymyositis and dermatomyositis (First of two parts), N. Engl. J. Med. 292 (1975) 344–347.
[11] A. Bohan, J.B. Peter, Polymyositis and dermatomyositis (Second of two parts), N. Engl. J. Med. 292 (1975) 403–407.
[12] R.D. Sontheimer, Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis, Curr. Opin. Rheumatol. 11 (1999) 475–482.
[13] T. Suda, T. Fujisawa, N. Enomoto, Y. Nakamura, N. Inui, T. Naito, et al., Interstitial lung diseases associated with amyopathic dermatomyositis, Eur. Respir. J. 28 (2006) 1005–1012.
[14] A. Ghirardello, M. Rampudda, L. Ekholm, N. Bassi, E. Tarricone, S. Zampieri, et al., Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay, Rheumatol. Oxf. 49 (2010) 2370, e2374.
[15] B. Ley, B.M. Elicker, T.E. Hartman, C.J. Ryerson, E. Vittinghoff, J.H. Ryu, et al., Idiopathic pulmonary fibrosis: CT and risk of death, Radiology 273 (2014) 570–579.
[16] W.D. Travis, U. Costabel, D.M. Hansell, T.E. Jr King, D.A. Lynch, A.G. Nicholson, et al., An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 188 (2013) 733–748.
[17] A. Fischer, K.M. Antoniou, K.K. Brown, J. Cadranel, T.J. Corte, R.M. du Bois, et al., ERS/ATS task force on undifferentiated forms of CTD-ILD. An official European respiratory society/American thoracic society research statement: interstitial pneumonia with autoimmune features, Eur. Respir. J. 46 (2015) 976–987.
[18] D.M. Hansell, A.A. Bankier, H. MacMahon, T.C. McLoud, N.L. Müller, J. Remy, Fleischner Society: glossary of terms for thoracic imaging, Radiology 246 (2008) 697–722.
[19] D.A. Lynch, N. Sverzellati, W.D. Travis, K.K. Brown, T.V. Colby, J.R. Galvin, et al., Diagnostic criteria for idiopathic pulmonary fibrosis: a fleischner society white paper, Lancet Respir. Med. 6 (2018) 138–153.
[20] M. Akira, Y. Inoue, T. Arai, T. Okuma, Y. Kawata, Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia, Thorax 66 (2011) 61–65.
[21] H. Liu, S. Xie, T. Liang, L. Ma, H. Sun, H. Dai, et al., Prognostic factors of interstitial lung disease progression at sequential HRCT in anti-synthetase syndrome, Eur. Radiol. 29 (2019) 5349–5357.
[22] H. Hozumi, T. Fujisawa, R. Nakashima, H. Yasui, Y. Suzuki, M. Kono, et al., Efficacy of glucocorticoids and calcineurin inhibitors for anti-aminoacyl-tRNA synthetase antibody-positive polymyositis/dermatomyositis-associated interstitial lung disease: a propensity score-matched analysis, J. Rheumatol. 46 (2019) 509–517.
[23] I.N. Targoff, E.P. Trieu, P.H. Plotz, F.W. Miller, Antibodies to glycyl-transfer RNA synthetase in patients with myositis and interstitial lung disease, Arthritis Rheum. 35 (1992) 821–830.
[24] Y. Hamaguchi, M. Fujimoto, T. Matsushita, K. Kaji, K. Komura, M. Hasegawa, et al., Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome, PloS One 8 (2013), e60442.
[25] J. Shi, S. Li, H. Yang, Y. Zhang, Q. Peng, X. Lu, et al., Clinical profiles and prognosis of patients with distinct antisynthetase autoantibodies, J. Rheumatol. 44 (2017) 1051–1057.

[26] S. Li, Y. Ge, H. Yang, T. Wang, X. Zheng, Q. Peng, et al., The spectrum and clinical significance of myositis-specific autoantibodies in Chinese patients with idiopathic inflammatory myopathies, Clin. Rheumatol. 38 (2019) 2171–2179.
[27] M. Giannini, A. Notarnicola, M. Dastmalchi, I.E. Lundberg, G. Lopalco, F. Iannone, Heterogeneous clinical spectrum of interstitial lung disease in patients with anti-EJ anti-synthetase syndrome: a case series, Clin. Rheumatol. 35 (2016) 2363–2367.
[28] C. Johnson, G.R. Connors, J. Oaks, S. Han, A. Truong, B. Richardson, et al., Clinical and pathologic differences in interstitial lung disease based on antisynthetase antibody type, Respir. Med. 108 (2014) 1542–1548.
[29] F. Schneider, S.A. Yousem, D. Bi, K.F. Gibson, C.V. Oddis, R. Aggarwal, Pulmonary pathologic manifestations of anti-glycyl-tRNA synthetase (anti-EJ)-related inflammatory myopathy, J. Clin. Pathol. 67 (2014) 678–683.
[30] H. Hane, Y. Muro, K. Watanabe, Y. Ogawa, K. Sugiura, M. Akiyama, Establishment of an ELISA to detect anti-glycyl-tRNA synthetase antibody (anti-EJ), a serological marker of dermatomyositis/polymyositis and interstitial lung disease, Clin. Chim. Acta 431 (2014) 9–14.
[31] C. Vitali, S. Bombardieri, R. Jonson, H.M. Moutsopoulos, E.L. Alexander, S. E. Carsons, et al., Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European consensus group, Ann. Rheum. Dis. 61 (2002) 544–548.
[32] A. Labirua-Iturburu, A. Selva-O'Callaghan, M. Vincze, K. Dankó, J. Vencovsky, B. Fisher, et al., Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature, Medicine (Baltim.) 91 (2012) 206.
[33] Y. Yamasaki, M. Satoh, M. Mizushima, T. Okazaki, H. Nagafuchi, S. Ooka, et al., Clinical subsets associated with different anti-aminoacyl transfer RNA synthetase antibodies and their association with coexisting anti-Ro52, Mod. Rheumatol. 26 (2016) 403–409.
[34] S.A. Rutjes, W.T. Vree Egberts, P. Jongen, F. Van Den Hoogen, G.J. Pruijn, W. J. Van Venrooij, Anti-Ro52 antibodies frequently co-occur with anti-Jo-1 antibodies in sera from patients with idiopathic inflammatory myopathy, Clin. Exp. Immunol. 109 (1997) 32–40.
[35] E. Trallero-Araguás, J.M. Grau-Junyent, A. Labirua-Iturburu, F.J. García-Hernández, M. Monteagudo-Jiménez, G. Fraile-Rodriguez, et al., Clinical manifestations and long-term outcome of anti-Jo1 antisynthetase patients in a large cohort of Spanish patients from the GEAS-IIM group, Semin. Arthritis Rheum. 46 (2016) 225–231.
[36] M.G. Cruellas, S. Viana Vdos, M. Levy-Neto, F.H. Souza, S.K. Shinjo, Myositis-specific and myositis-associated autoantibody profiles and their clinical associations in a large series of patients with polymyositis and dermatomyositis, Clinics. (Sao Paulo) 68 (2013) 909–1014.
[37] R. La Corte, A. Lo Mo Naco, A. Locaputo, F. Dolzani, F. Trotta, In patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease, Autoimmunity 39 (2006) 249–253.